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(54) Stable, aqueous, solubilized materials comprising carotinoids and vitamins

(57) Stable, aqueous, solubilized materials, which are suitable for parenteral administration, comprising carotinoids and vitamins or vitamin derivatives in which the carotinoid and water-insoluble vitamins are dissolved, in the form of micelles, with the help of a non-ionogenic emulsifier, whereby the micelles are smaller than 100 nm, and whereby the solubilized materials contain the following in the indicated quantities based on the solubilized material: at least one carotinoid at a concentration of 0.1 to 10% by weight; water-insoluble lipophilic vitamins or vitamin derivatives at a concentration of 0.1 to 20% by weight; and non-ionogenic emulsifiers at a concentration of 1 to 40% by weight, with the proviso that the concentration of the lipophilic vitamins is at least as great as that of the carotinoid.

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Specification

The invention pertains to stable, aqueous, solubilized materials, which are suitable for parenteral administration, comprising carotinoids and vitamins, that are prepared with the help of non-ionogenic emulsifiers.

Carotinoids, vitamins and trace elements are of great importance from the nutritional physiological standpoint. An insufficient supply thereof leads to deficiency phenomena in the human and animal organism. In the case of some diseases, patients are unable to take any food or medications by mouth but, rather, they have to be fed parenterally. In these cases, the above-mentioned substances have to be supplied in this [parenteral] manner as well. Moreover, cases are also encountered in which patients are markedly depleted in regard to carotinoids, vitamins and trace elements even with oral feeding, so that rapid restoration of their physiological concentrations is desirable. Parenteral administration is also indicated in such cases. In the case of the application of quantities, which go beyond their physiological values, moreover, some carotinoids, vitamins and trace elements are attributed with preventive effects in regard to various diseases such as atherosclerosis, heart infarction, stroke, macular degeneration, cataracts, Parkinson's disease, and cancer. In this connection, it is assumed that the anti-oxidative, radical-trapping properties of these substances are responsible for these effects since it is known that oxidative agents and radicals lead to cellular changes. In addition, these compounds, which are essential for humans, allegedly strengthen the immune system. Thus an increase in T-lymphocytes, especially T-helper cells, has occurred as a result of the administration of vitamin E.

β-carotin and additional carotinoids, tocopherol or tocopherol derivatives, ascorbic acid or ascorbic acid derivatives and selenium compounds are of special significance in this connection. A combination of these substances or some of these substances is usually termed an antioxidant combination.

Up to this point in time, no formulation is available for parenteral application that permits quantities of the aforementioned carotinoids and vitamins to be administered that go beyond their physiological or super-physiological values.

Solubilized β-carotin materials are known from European patent specifications EP 0 055 817 and the unexamined patent application ["Offenlegungsschrift"] DE 40 31 094 A1 that contain a non-ionogenic surfactant as a solubilizer with an HLB value of 12 to 16.

The preparation of a solubilized material from β-carotin and an emulsifier with an HLB value of 10 to 18 is described in PCT application WO 94 06 310 A1, whereby this solubilized material is used in foodstuffs for coloring purposes. As is usual, small quantities of antioxidants can be added to the preparation in order to stabilize the β-carotin.

The problem arose of proposing solubilized materials that contain both β-carotin and vitamins, are stable with respect to precipitation, and are suitable for parenteral administration. It was therefore to be expected that the incorporation of additional lipophilic components in quantities that are at least as large as, or larger than, the quantity of β-carotin will disrupt the micellar structure of the solubilized β-carotin in such a way that precipitation of the β-carotin occurs, whereby this is water-insoluble as such. A disruption was also to be expected from larger quantities of water-soluble vitamins that are generally present in salt form.

Surprisingly, it has now been found that aqueous solubilized materials from carotinoids and vitamins or vitamin derivatives, which are suitable for parenteral administration and in which the carotinoid and the water-insoluble vitamins are dissolved in micellar form with the help of a non-ionogenic emulsifier, whereby the micelles are smaller than 100 nm and are completely stable physically and chemically over an extended period of time, whereby the solubilized materials, in quantities based on the solubilized material, contain at least one carotinoid at a concentration of 0.1 to 10% by weight, the water-insoluble lipophilic vitamins or vitamin derivatives at a concentration of 0.1 to 20% by weight and the non-ionogenic emulsifiers at a concentration of 1 to 40% by weight, with the proviso that the concentration of the lipophilic vitamins is at least as great as that of the carotinoid.

It has also been found that - because of unexpected interactions between the carotinoids, the lipophilic vitamins and, especially, tocopherol or tocopherol esters and the non-ionic surfactant - the quantity of non-ionic surfactant in the mixture can be kept lower than corresponds to the sum of the solubilized materials with the individual active substances. The preparation becomes locally and systemically tolerable for humans as a result. In addition, there is the feature that, surprisingly, the combination of carotinoids with lipophilic vitamins permits temperature stressing of the carotinoids and thus possible decomposition is to be reduced during the preparation procedure. Solubilization proceeds more rapidly than without the addition of the lipophilic vitamin.

This surprising finding of superb stabilization is expected to result from the formation of mixed micelles in which interactions are possible at the molecular level.

The solubilized materials generally have average particle sizes of 5 to 100 nm for the micelles. These particle sizes are thus far smaller than the minimum requirement of 1 μm for injection emulsions.

Physiologically tolerable compounds, which are known as such and especially those with an HLB value of 10 to 20, can be considered as the non-ionogenic emulsifiers. In terms of details, mention may be made of polyoxyethylene glycerol triricinoleate with 20 to 60 oxyethylene units; polyoxyethylene-12-hydroxystearate with 10 to 40 oxyethylene units; polyoxyethylene sorbitan fatty acid esters with 10 to 40 oxyethylene units; and polyoxyethylene-polyoxypropylene block copolymers with the formula

[formula; page 3]

in which a and c signify 10 to 130 and, preferably, approximately 80, and b signifies 15 to 70 and, preferably, approximately 30 units.

β-carotin, in particular, and also lycopine, astaxanthin, canthaxanthin, citranaxanthin, zeaxanthin, apocarotinol and/or apocarotinic acid esters can be considered as the carotinoids; tocopherol, tocopherol acetate, tocopherol succinate, retinal, retinol, retinol esters, retinic acid, cholecalciferol and/or ergocalciferol can be considered as the lipophilic vitamins.

Based on the solubilized material, the carotinoids are preferably present in quantities of 0.4 to 6% by weight, and the lipophilic vitamins are preferably present in quantities of 0.4 to 10% by weight, and the emulsifiers are preferably present in quantities of 5 to 25% by weight.

Naturally, the solubilized materials can also be diluted further with a physiologically tolerable vehicle for use in the form of ampoules, ready-to-use syringes, infusion solutions, solutions for drop application, or syrups.

In addition, hydrophilic vitamins, such as vitamin C or the vitamins of the B series as well as mineral substances, if required, and trace elements, such as selenium compounds, can be present in the aqueous phase. Finally, further pharmaceutically active substances, such as N-acetylcysteine, can be present in the solubilized materials.

A preferred antioxidant combination contains β-carotin, tocopherol or the tocopherol esters, ascorbic acid and, optionally, selenium compounds and N-acetylcysteine.

The manufacture of the preparations in accordance with the invention generally takes place in such a way that the carotinoid is briefly heated with the lipophilic vitamins and the emulsifier to temperatures in excess of 1200°C [sic] and, as a result, it goes into solution, and it is then immediately mixed with a solution in water of the hydrophilic substances that are used, or a buffer solution, and it is thereby cooled. Alternatively, mixing can also take place with water or a buffer solution, and the hydrophilic vitamins can be added subsequently. A further possibility comprises briefly heating the carotinoid with the emulsifier to temperatures in excess of 1200°C [sic], and mixing this solution with a solubilized material comprising

lipophilic vitamins in water or in a buffer, whereby this solubilized material had been prepared separately in a known way.

The preferred preparation is carried out discontinuously using the process of EP 0 055 817 and, in particular, continuously using the process of EP 0 479 066. Thus reference is made explicitly to these two patent specifications, and to the conditions that are indicated therein.

If it is to be used for parental purposes, then, after cooling, the solubilized material is filtered in a sterile manner, e.g. through a 0.22 µm filter, and then it is tapped off into ampoules, ready-to-use syringes, vials or infusion bottles. Sterile filtration can be omitted in the case of oral administration, and the solubilized material is packaged in drop-application bottles or syrup bottles. In this case it is advantageous if sweetening agents and aroma-enhancing agents are added during the manufacture of the solubilized material, or subsequently, in order to improve its taste.

Examples

Example 1

23.0 g of polyoxyethylene-12-hydroxystearate with 15 oxyethylene units (Solutol® HS 15), 5.0 g of tocopherol acetate, and 0.5 g of butylhydroxytoluene were introduced into a flask, which was being flushed out with nitrogen gas, and heated to 180°C. 6.0 g of β-carotin were then dissolved [in this mixture] with stirring; the source of heating was then removed, and the hot mixture was mixed, under turbulent conditions, with a solution, which had been warmed to approximately 20°C, comprising 4.9 g of sodium ascorbate and 0.1 g of ascorbic acid in 60.5 g of water for injection purposes. A clear, deep red, thinly fluid, solubilized material was formed in this way, and this was filtered through a filter with a pore width of 0.45 µm, and tapped off into vials with rubber stoppers.

β-carotin concentration:	5.8%
tocopherol acetate concentration:	5.1%
ascorbic acid concentration:	4.2%
micelle size:	32 nm
pH value:	5.8

The preparation was also absolutely clear, and unchanged in terms of its concentration values, after 6 months of storage at room temperature and at 30°C.

Example 2

23.0 g of Solutol® HS 15 and 5.0 g of tocopherol acetate were heated to 180°C in a flask that was being flushed out with nitrogen gas. 4.0 g of β-carotin were then dissolved [in this mixture] with stirring, the source of heating was removed, and the hot mixture was mixed with a solution, which had been warmed to 20°C, comprising 4.9 g of sodium ascorbate and 0.1 g of ascorbic acid in 63.0 g of water for injection purposes. A clear, deep red, thinly fluid, solubilized material was formed in this way and this was filtered through a filter with a pore width of 0.45 µm, and tapped off into vials with rubber stoppers.

The preparation was also absolutely clear and unchanged in terms of its concentration values after 6 months of storage at room temperature and at 30°C.

β-carotin concentration:	3.9%
tocopherol acetate concentration:	5.2%
ascorbic acid concentration:	4.3%
micelle size:	27 nm
pH value:	6.0

Example 3

23.0 g of Solutol® HS 15, and 10.0 g of tocopherol acetate, and 0.5 g of tocopherol were heated to 180°C in a flask that was being flushed out with nitrogen gas. 6.0 g of β-carotin were then dissolved [in this mixture] with stirring, the source of heating was removed and the hot mixture was mixed with a solution, which had been warmed to 20°C, comprising 5.5 g of sodium ascorbate and 0.1 g of ascorbic acid in 54.0 g of water for injection purposes. After cooling to room temperature, the clear, deep red, solubilized material was filtered through a filter with a pore width of 0.45 µm and then tapped off into ampoules.

β-carotin concentration:	5.7%
tocopherol acetate concentration:	10.4%
ascorbic acid concentration:	5.1%
micelle size:	42 nm
pH value:	6.0

Example 4

Continuous preparation

A suspension of 40 g of β-carotin in 250 g of Solutol® HS 15, 50 g of tocopherol acetate, and 10 g of butylhydroxytoluene were introduced into a heated receptacle. The suspension was pumped into a calorifier, which was immersed in an oil bath, by means of a high pressure pump using a throughput rate of 2 l/h. The dwell time was adjusted to 34 seconds for an internal diameter of 2 mm and a length of 6 m using heat transfer oil temperatures of 170°C. This time is sufficient to dissolve the β-carotin. After the designated dwell time in the calorifier, the β-carotin solution entered a T-shaped mixing chamber and was turbulently mixed therein with an aqueous solution comprising 6.8% sodium ascorbate, 0.2% ascorbic acid and 0.01% Thimerosal, at a mixing angle of 180°, by means of a high pressure pump using a throughput rate of 4.7 l/h. The product was removed via a pressure limiter valve at a pressure of 25 bar. A dark red colored micellar antioxidant solution was obtained.

After filtration through a 0.45 µm filter, the solubilized material was tapped off into vials with rubber stoppers while flushing out with nitrogen gas.

β-carotin concentration:	3.3%
tocopherol acetate concentration:	4.3%
ascorbic acid concentration:	4.3%
micelle size:	28 nm
pH value:	5.9

Example 5

13.0 g of Solutol® HS 15 and 0.5 g of tocopherol were introduced into a flask, which was being flushed out with nitrogen gas, and heated to 180°C. 4.0 g of β-carotin were then dissolved [in this mixture] with stirring, the source of heating was removed and the hot mixture was mixed with 82.5 g of a solubilized material comprising tocopherol acetate / ascorbic acid that had been prepared separately.

In order to prepare the solubilized material that comprised tocopherol acetate / ascorbic acid, 5.0 g of tocopherol acetate were mixed with 10.0 g of Solutol® HS 15 and heated to 65°C. A solution of 4.9 g of sodium acetate and 0.1 g of ascorbic acid in 62.5 g of demineralized water were slowly incorporated into this mixture with intimate stirring.

After cooling to room temperature, the clear, deep red, antioxidant solubilized material was filtered through a 0.45 µm filter and tapped off into vials with rubber stoppers.

β-carotin concentration:	3.9%
tocopherol acetate concentration:	5.2%
ascorbic acid concentration:	4.3%
micelle size:	29 nm
pH value:	6.1

Example 6

20.0 g of tocopherol acetate and 0.5 g of tocopherol were mixed with 200 g of Solutol® HS 15 in a receptacle that was being thermostatically heated to 80°C. 10.0 g of β-carotin were then suspended uniformly [therein] while flushing out with nitrogen gas. The suspension was fed to a calorifier, which was immersed in an oil bath, by means of a high pressure pump at a throughput rate of 2 l/h. The temperature of the heating bath amounts to 170°C, and the dwell time in the calorifier amounts to approximately 34 seconds. After leaving the calorifier, the clear red solution was collected in a flask that was being flushed out with nitrogen gas. A separately prepared solution of 100.0 g of sodium ascorbate, 40.0 g of nicotinamide, 15.0 g of pyridoxine HCl, 10.0 g of sodium riboflavin-5-phosphate x 2 H_2O, 10.0 g of thiamine-HCl and 25.0 g of dexpanthenol in a mixture comprising 406.0 g of 0.1 molar caustic soda solution and 1,164.0 g of water for injection purposes was then slowly stirred into this solution, and the preparation was cooled to room temperature and filtered through a 0.45 µm filter.

β-carotin concentration:	0.48%
tocopherol acetate concentration:	1.05%
sodium ascorbate concentration:	4.9%
sodium riboflavin-5-phosphate x 2 H_2O concentration:	0.50%
thiamine-HCl concentration:	0.46%
nicotinamide concentration:	2.10%
pyridoxine-HCl concentration:	0.74%
micelle size:	19 nm
pH value:	5.5

Example 7 (comparison example)

The following experiments were carried out using the continuous method of preparation as described in Example 4:

Recipe A:	β-carotin	6%
	Solutol® HS 15	23%
	water for injection purposes to	100%
Recipe B:	β-carotin	6%
	tocopherol	1.2%
	Solutol® HS 15	23%
	water for injection purposes to	100%
Recipe C:	β-carotin	6%
	tocopherol acetate	10%
	Solutol® HS 15	23%
	water for injection purposes to	100%

The oil bath temperature amounted to 170°C in each case.

Results:

Recipe A: turbid solubilized material that was not adequately stable

Recipe B: turbid solubilized material that was not adequately stable

Recipe C: clear, stable solubilized material

Example 8

23.0 g of Solutol® HS 15 and 5 g of tocopherol were heated to 180°C in a flask that was being flushed out with nitrogen gas. 4.0 g of β-carotin were then dissolved [in this mixture] with stirring, the source of heating was removed and the hot mixture was mixed with a solution, which had been warmed to 20°C, comprising 5.5 g of sodium ascorbate and 0.1 g of ascorbic acid in 62.4 g of water for injection purposes. After cooling to room temperature, the clear, deep red, solubilized material was filtered through a filter with a pore width of 0.45 µm and then tapped off into vials.

β-carotin concentration:	3.8%
tocopherol concentration:	5.0%
ascorbic acid concentration:	5.2%
micelle size:	27 nm
pH value:	6.0

Example 9

A suspension of 16 g of astaxanthin in 400 g of Solutol® HS 15 and 32 g of tocopherol acetate were introduced, at a temperature of 60°C, into the mixing system analogously to the continuous method of preparation that was described in Example 4. The suspension was led through a calorifier, which was immersed in an oil bath at a temperature of approximately 210°C, at a throughput rate of 2.2 l/h, whereby the calorifier had an internal diameter of 2 mm and a length of 12 m. The dwell time, which had been adjusted to 62 seconds in this way, was sufficient to dissolve the astaxanthin in the emulsifier. An aqueous solution comprising 1.5 g/l of ascorbic acid and 37 g/l of sodium ascorbate was then mixed [with this mixture], under turbulent conditions in the mixing chamber, using a throughout rate of 5.4 l/h. The product was removed at a pressure of 30 bar via a pressure limiter valve. A dark red colored, micellar astaxanthin solution was obtained that was filtered through a 0.22 µm filter.

astaxanthin concentration:	0.8%
tocopherol acetate concentration:	2.0%
concentration of sodium ascorbate + ascorbic acid:	2.7%
micelle size:	30 nm
pH value:	5.9

Patent claims

1. Stable, aqueous, solubilized materials, which are suitable for parenteral administration, comprising carotinoids and vitamins or vitamin derivatives, in which the carotinoid and water-insoluble vitamins are dissolved in the form of micelles with the help of a non-ionogenic emulsifier, whereby the micelles are smaller than 100 nm, characterized by the feature that the solubilized materials contain the following in the indicated quantities based on the solubilized material: at least one carotinoid at a concentration of 0.1 to 10% by weight; water-insoluble lipophilic vitamins or vitamin derivatives at a concentration of 0.1 to 20% by weight; and non-ionogenic emulsifiers at a concentration of 1 to 40% by weight, with the proviso that the concentration of the lipophilic vitamins is at least as great as that of the carotinoid.

2. Stable, solubilized materials in accordance with Claim 1, characterized by the feature that the concentration of the carotinoid amounts to 0.4 to 6% by weight, and that of the lipophilic vitamins amounts to 0.4 to 10% by weight, and that of the non-ionogenic emulsifiers amounts to 5 to 25% by weight.

3. Stable, solubilized materials in accordance with Claim 1, characterized by the feature that they contain carotinoids, lipophilic vitamins, hydrophilic vitamins, and also mineral substances if required.

4. Solubilized materials in accordance with Claim 1, characterized by the feature that they contain a carotinoid, tocopherol or a tocopherol ester, ascorbic acid and selenium compounds and N-acetylcysteine as well if required.

5. Solubilized materials in accordance with Claim 1, characterized by the feature that they contain: β-carotin, lycopine, astaxanthin, canthaxanthin, citranaxanthin, zeaxanthin, apocarotinol and/or apocarotinic acid esters as the carotinoids; and tocopherol, tocopherol acetate, tocopherol succinate, retinal, retinol, retinol esters, retinic acid, cholecalciferol and/or ergocalciferol as the lipophilic vitamins; and non-ionogenic solubilizers with an HLB value of 10 to 20 as the non-ionogenic solubilizers, whereby these are selected from the group comprising polyoxyethylene glycerol triricinoleate, polyoxyethylene-12-hydroxystearate, polyoxyethylene sorbitan fatty acid esters, and polyoxyethylene/polyoxypropylene block copolymers.

6. Solubilized materials in accordance with Claim 1, characterized by the feature that, directly or after dilution with a physiologically tolerable vehicle, they are present in the form of ampoules, ready-to-use syringes, infusion solutions, solutions for drop application, or syrups.

7. Process for the preparation of solubilized materials in accordance with Claim 1, characterized by the feature that the carotinoid is briefly heated with the lipophilic vitamins or vitamin derivatives and the non-ionogenic emulsifier to temperatures in excess of 120°C until dissolution takes place, and then [the mixture] is immediately mixed with water, or an aqueous solution of the hydrophilic components, under turbulent conditions and the mixture is then cooled.

8. Process for the preparation of solubilized materials in accordance with Claim 1, characterized by the feature that only the carotinoid is briefly heated with the non-ionogenic emulsifier to temperatures in excess of 120°C until dissolution takes place, and then [the mixture] is immediately mixed, under turbulent conditions, with a separately prepared solubilized material comprising lipophilic vitamins, and the mixture is then cooled.

European Patent Office

Application number
EP 97 10 3484

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.[6])
X	WO 95 18605 A (MARIGEN SA; EUGSTER CARL (SWITZERLAND); EUGSTER CONRAD HANS (SWITZERLAND); HALDEMANN) July 13, 1995 * see Doc., page 21, lines 6-11, page 35, "Zusammensetzung..", pg. 9, last par. claim 1*	1-8	A61K31/07 A61K31/355 A61K31/375 A61K9/08
D,X	EP 0 479 066 A (BASF AG) April 8, 1992, * page 2, last paragraph, pg. 3, lines 8-9 and also the example*	1-8	
A	WO 94 06310 A (SMITHKLINE BEECHAM PLC; FORD MICHAEL ANTHONY (GREAT BRITAIN); MELLOR CLIVE (GREAT [BRITAIN]) March 31, 1994 * see abstract, pg. 3, par. 1-4 and pg. 8, example 2*	1-8	
A,D	DE 40 31 094 A (BASF AG) April 9, 1992 * see example on pg. 3 and claims 1-7*	1-8	

TECHNICAL FIELDS SEARCHED (Int. Cl.[6])

A61K

The present search report has been drawn up for all claims.

Place of search	Search completion date	Examiner
MUNICH	July 29, 1997	Stoltner, A

CATEGORY OF CITED DOCUMENTS

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